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Atopic conditions and brain tumor risk in children and adolescents—an international case–control study (CEFALO)

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Background: A number of epidemiological studies indicate an inverse association between atopy and brain tumors in adults, particularly gliomas. We investigated the association between atopic disorders and intracranial brain tumors in children and adolescents, using international collaborative CEFALO data.

Patients and methods: CEFALO is a population-based case–control study conducted in Denmark, Norway, Sweden, and Switzerland, including all children and adolescents in the age range 7–19 years diagnosed with a primary brain tumor between 2004 and 2008. Two controls per case were randomly selected from population registers matched on age, sex, and geographic region. Information about atopic conditions and potential confounders was collected through personal interviews.

Results: In total, 352 cases (83%) and 646 controls (71%) participated in the study. For all brain tumors combined, there was no association between ever having had an atopic disorder and brain tumor risk [odds ratio 1.03; 95% confidence interval (CI) 0.70–1.34]. The OR was 0.76 (95% CI 0.53–1.11) for a current atopic condition (in the year before diagnosis) and 1.22 (95% CI 0.86–1.74) for an atopic condition in the past. Similar results were observed for glioma.

Conclusions: There was no association between atopic conditions and risk of all brain tumors combined or of glioma in particular. Stratification on current or past atopic conditions suggested the possibility of reverse causality, but may also the result of random variation because of small numbers in subgroups. In addition, an ongoing tumor treatment may affect the manifestation of atopic conditions, which could possibly affect recall when reporting about a history of atopic diseases. Only a few studies on atopic conditions and pediatric brain tumors are currently available, and the evidence is conflicting.

Key words: allergy, brain tumors, case–control study, childhood, glioma

introduction

Brain tumors account for the largest number of cancer deaths in children, the second most common group of neoplasms, and the largest group of pediatric solid tumors in developed countries [1, 2]. Despite extensive research, the etiology of childhood brain tumors remains largely unknown. The only established risk factors are high doses of ionizing radiation, and rare genetic disorders such as neurofibromatosis I or Li–Fraumeni syndrome [3–5]. However, these explain only a small fraction of the cases.

Epidemiological studies in adults have consistently reported that atopic conditions, such as asthma, hay fever, or eczema, are inversely associated with the risk of glioma but not consistently with meningioma [6–8]. To date, there are only two studies available on atopic conditions and brain tumors in childhood [9, 10], with results compatible with those in adults.

The biological mechanism underlying this association is yet to be elucidated. Two main hypotheses have been proposed: the first one, the immune surveillance hypothesis claims that the presence of an atopic condition increases the immune system surveillance to detect and eliminate malignant cells, contributing to

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prevention of potential cancers [11–13]. The second hypothesis claims that the association is reverse causality. The tumor itself is known to be immunosuppressive, by affecting the balance between Th1 and Th2 cytokines [14], and could potentially prevent or mitigate atopic symptoms. This would lead to a lower prevalence or decreased severity of atopic conditions among brain tumor patients, including yet undiagnosed ones.

The aim of this study was to examine the association between atopic conditions including asthma, wheezing, eczema, and allergic rhinitis, and risk of intracranial brain tumors in children and adolescents.

material and methods

The CEFALO study is a population-based multicenter case–control study carried out in Denmark, Norway, Sweden, and Switzerland. The study period was from 1 January 2004 through 31 August 2008, with slight time variations between countries (Table 1).

case eligibility and ascertainment

Eligible cases were all children and adolescents diagnosed during the study period with primary intracranial brain tumors in the age range 7–19 years. All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. Medical records for cases were examined to confirm diagnosis and establish the date of diagnosis. The completeness of case ascertainment was verified through searches in the population-based cancer registries according to country-specific procedures. Brain tumors were classified according to the International Classification of Diseases tenth revision (ICD-10). Case recruitment and tumor classification are described in detail in Aydin et al. [15].

control eligibility and selection

Two controls per case were randomly selected from population registers in the participating countries, matched on age, sex, and geographic region. In Switzerland, a two-stage sampling procedure was applied for the selection of controls in the absence of a national population registry. First, community was randomly selected within the same language region as the case and second, the control was randomly selected from the corresponding communal population registry. The reference date for controls was the date of diagnosis of the matched case.

exclusion criteria

Cases and controls diagnosed with neurofibromatosis (Mb Recklinghausen) or tuberose sclerosis, or completely deaf before the reference date or with severe mental retardation were excluded. Additionally, families with insufficient language skills to complete an interview were excluded, as judged by the nurse, treating physician, or project administrator.

data collection

Data collection started in June 2006 in all countries except Norway, where it started in December 2007. Physician authorization for contact was obtained for all cases, and both cases and controls provided signed informed consent. The procedures varied between countries, depending on the requirements of local ethics review boards. If the case was deceased, the parents were contacted at the earliest 6 months after the death of the child.

Whenever possible, the child and at least one of the parents were interviewed face-to-face by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire (Denmark and Norway) or a paper version of the questionnaire (Switzerland and Sweden). In exceptional cases, telephone interviews were conducted with difficult-to-reach subjects (4 controls) or an adjusted paper version of the questionnaire was sent to the study participant (19 controls). All interviews and contacts with the cases and controls were made by interviewers employed for this purpose. Interviewers from all centers received training at a joint workshop to ensure uniform data collection. The translations of the questionnaire were checked through back-translation to the master version (English), and the questionnaires were pilot tested in all participating countries. The interviewer was not blinded regarding the disease status. Interviews with a case and matched controls were mainly carried out by the same interviewer.

The core questions used in the CEFALO study to identify atopic conditions are based on the International study of asthma and allergies in childhood (ISAAC) [16]. The definitions of the atopic conditions are described in the EAppendix. Categorization of atopic conditions was ascertained through questions on whether the child had ever been diagnosed by a medical doctor with asthma (ever/never), eczema (ever/never), or allergic rhinitis (ever/never). Wheezing disorder (ever/never) was identified through a positive answer on questions whether the child ever had wheezing or whistling in the chest at any time in the past, but was not diagnosed with asthma. If the participant answered 'ever', exposure status of this subject was further categorized as 'current' if the child had at least one episode of the atopic condition in the last 12 months before the diagnosis/reference date, or 'past' if the child did not have any episode of the atopic condition in the last 12 months.

statistical methods

Estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using conditional logistic regression for individually matched datasets. ORs were calculated for all atopic conditions combined, for specific atopic conditions separately, and for 'current' and 'past' status of the atopic

Table 1. Descriptive characteristics of participants by study center, the CEFALO study

	Denmark	Norway	Sweden	Switzerland	All countries
Study period	January 2004 to April 2008	September 2004 to August 2008	April 2004 to August 2008	May 2004 to May 2008	
Interviewed cases (participation rate, %)	85 (98)	44 (66)	138 (85)	85 (80)	352 (83)
Proxy interviews for diseased cases (participation rate, %)	*10 (12)*	*9 (20)*	*9 (7)*	*8 (9)*	*36 (10)*
Interviewed controlsa (participation rate, %)	170 (73)	78 (58)	228 (76)	170 (70)	646 (71)

Italic values show the number of case and percentage of proxy respondents in cases.
[a]No proxy interviews were made for controls.

conditions. The reference category consisted of children who had reported no atopic condition at all. The analyses were made for all brain tumors combined, and for glioma (ICD-O-3 morphology code: 9380-84, 9390-9393, 9400-9401, 9410-9411, 9420-9424, 9430, 9440-9442, 9444, 9450-9451, 9460) and 'other brain tumors'.

We tested the impact of potential confounders, such as family history of cancer (yes/no), past medical radiation exposure to the head (yes/no), smoking of the mother during pregnancy (yes/no), past head injuries (yes/no), and infections (yes/no). Confounders that changed the OR by 10% or more were included in the final model. Adjustments for the child living on a farm before the age of 6 years (yes/no) and for socioeconomic status were made in all analyses.

All analyses were carried out using SAS statistical package v 9.3. (SAS Institute, Inc., Cary, NC).

results

The distribution of cases and controls by study centers is shown in Table 1. A total of 352 cases (83% of eligible) and 646 controls (71%) participated in the study. Proxy respondents of the children were interviewed for 10% of participating cases. The time lag between date of interview and date of diagnosis (reference date for control) ranged from 2 to 56 months for cases, and 2 to 57 months for controls, with the 25th, 50th, and 75th percentiles at 11, 18, and 31 months for cases, and 12, 20, and 32 months for controls.

Of the 352 participating cases, 83% were confirmed by histopathological examination. The majority of cases were diagnosed with glioma (60%), with astrocytoma being the largest subgroup (Table 2). Proportions of PNET in the group 'other brain tumors' were 50% for cases below 15 years at diagnosis and 33% for older cases.

Ever having had any of the atopic conditions was reported by 46% of both cases and controls. Asthma was reported by 13% of cases and controls, while eczema was reported by 21% of cases and 20% of controls. The results did not show an association between ever having had an atopic condition and all brain tumors combined or with glioma only, while a slightly but non-significantly reduced OR was observed for 'other brain tumors' (Table 3). ORs associated with specific types of atopic conditions with all brain tumors combined or with glioma only were all close to unity, but slightly lower effect estimates were observed for 'other brain tumors', especially with eczema and allergic rhinitis.

Effect estimates for all brain tumors combined or glioma with a current diagnosis of an atopic condition were consistently reduced, while effect estimates for those with a past atopic condition were slightly above unity, although with wide CIs (Table 4). A similar pattern was observed for the four specific types of atopic conditions. Further analysis of glioma demonstrated a lower risk in females than males; however, none reached statistical significance (data not shown).

discussion

In this population-based case–control study, we did not observe an association between ever having had an atopic condition and brain tumor risk in children and adolescents. There were indications of reduced risk associated with a current atopic condition, but this was accompanied by slightly raised risk for having had an atopic condition in the past.

The suggestion that atopic conditions may be associated with a reduced risk of developing brain tumors was introduced in the early 1990s [17], and has been investigated in adults mainly in case–control studies, but also a few cohort studies [6–8, 18, 19]. So far, there are only two case–control studies carried out among children, with main results compatible with the findings for adults [9, 10]. Our overall results are not in agreement with the two previous studies on children. Harding et al. [10] found greater risk reductions for PNET/medulloblastoma than for pilocytic astrocytoma or glioma, and similar findings were reported by Roncarolo et al. [9]. The older age-range included in our study, 7–19 years compared with 0–14 years in the two other studies might explain some of the differences, as the distribution of brain tumor subtypes differs between the studies. The number of children with PNET/medulloblastoma in our study was small, and was grouped into the category 'other tumors', where slightly reduced effect estimates were observed, but based on small numbers. Nevertheless, the distribution of histological subtypes of glioma in our study of 7–19 years olds differs considerably compared with adults. The main type of adult glioma

Table 2. Distribution of brain tumors subgroups by age at diagnosis and gender, the CEFALO study

	Age at diagnosis (years)				Gender				Total
	<15	%	15–20	%	Male	%	Female	%	
Glioma									
Ependymoma	12	7	8	2	11	3	9	3	20
Astrocytoma	110	28	51	14	86	24	75	21	161
Other gliomas	18	5	12	3	13	4	17	5	30
Other brain tumors									
PNET[a]	46	13	16	5	39	11	23	7	62
Other specified brain tumors	31	9	23	7	31	9	23	7	54
Unspecified brain tumors	15	4	10	3	10	3	15	4	25
Total	232	66	120	34	190	54	162	46	352

[a]Primitive neuroectodermal tumors.

Table 3. Atopic conditions and risk of brain tumors, the CEFALO study

	All brain tumors				Glioma (ependymoma, astrocytoma, other gliomas)				Other brain tumors (PNET, other specified brain tumors, unspecified brain tumors)			
	Cases ($N = 352$)	Controls ($N = 646$)	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Reference (no atopic condition)	191	349	1.00		106	205	1.00		85	144	1.00	
Any atopic condition												
Ever[b]	160	293	1.03	0.70–1.34	104	174	1.18	0.84–1.67	56	119	0.82	0.54–1.25
Number of atopic conditions												
One	103	190	1.01	0.75–1.36	62	115	1.09	0.74–1.60	41	75	0.90	0.57–1.43
Two or more	55	100	1.09	0.74–1.59	40	58	1.43	0.88–2.32	15	42	0.68	0.36–1.31
Type of atopic conditions												
Asthma												
Ever	47	85	0.95	0.60–1.49	32	49	0.99	0.54–1.82	15	36	0.85	0.41–1.76
Wheezing[c]												
Ever	41	78	1.19	0.72–1.96	23	43	1.23	0.59–2.57	18	35	1.16	0.58–2.31
Eczema												
Ever	75	127	1.01	0.69–1.48	52	72	1.37	0.85–2.22	23	55	0.60	0.31–1.17
Allergic rhinitis												
Ever	62	135	0.81	0.55–1.21	45	81	1.11	0.68–1.83	17	54	0.47	0.23–0.96

[a]Matched analyses adjusted for living on a farm before age 6 and socioeconomic status.
[b]One case and four controls were excluded because of missing information.
[c]Used for children with reported wheeze without a diagnosis of asthma.

Table 4. Current/past atopic condition and risk of brain tumors, the CEFALO study

	All brain tumors				Glioma (ependymoma, astrocytoma, other gliomas)				Other brain tumors (PNET, other specified brain tumors, unspecified brain tumors)			
	Cases ($N = 352$)	Controls ($N = 646$)	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Reference (no atopic condition)	191	349	1.00		106	205	1.00		85	144	1.00	
Any atopic condition[b]												
Current	57	134	0.76	0.53–1.11	37	86	0.81	0.50–1.29	20	48	0.69	0.38–1.27
Past	79	115	1.22	0.86–1.74	50	63	1.45	0.91–2.30	29	52	0.96	0.55–1.66
Type of atopic conditions												
Asthma												
Current	19	39	0.81	0.41–1.60	15	22	0.97	0.42–2.25	4	17	0.41	0.10–1.64
Past	20	36	1.00	0.51–1.95	13	22	0.89	0.36–2.22	7	14	1.01	0.35–2.89
Wheezing[c]												
Current	10	27	0.93	0.36–2.41	5	15	0.42	0.08–2.14	5	12	1.50	0.44–5.09
Past	29	40	1.33	0.74–2.39	16	20	1.75	0.70–4.36	13	20	1.12	0.51–2.48
Eczema												
Current	23	52	0.79	0.43–1.48	15	34	0.89	0.41–1.93	8	18	0.78	0.26–2.33
Past	31	44	1.17	0.65–2.09	20	23	1.75	0.76–3.29	11	21	0.58	0.21–1.61
Allergic rhinitis												
Current	46	105	0.76	0.48–1.19	33	61	1.10	0.62–1.96	13	44	0.39	0.17–0.86
Past	7	5	2.65	0.61–11.44	7	2	7.93	0.89–70.38	0	3		

[a]Matched analyses adjusted for living on a farm before age 6 and socioeconomic status.
[b]The number of 'current' and 'past' do not add up due to missing information on diagnosis date of atopic conditions.
[c]Used for children with reported wheeze without a diagnosis of asthma.

are stage 4 (>50% glioblastoma), and the rest are mainly stage 3 or 2, while most gliomas in children are stage 1 (pilocytic astrocytoma). Furthermore, there is evidence [20] that grade 1 glioma does not develop through the stages in children. This may explain the discrepancy observed between our previous study on adults [6] and the present study.

In our study on adults [6], we found that the reduced glioma risk was primarily associated with an ongoing atopic condition, whereas risk estimates were close to unity for individuals who had had an atopic condition in the past, but not at the time of glioma diagnosis. This finding was interpreted as being in agreement with the immune surveillance hypothesis, indicating that an active immune system might be protective. Caution was, however, expressed, as an alternative explanation could be reverse causation. The immunosuppressive effect of the tumor itself [21, 22] could make atopic conditions in cases disappear, and these subjects would consequently move to the 'past allergy' group. Accordingly, the expected pattern with brain tumor is an association below unity with current atopic conditions and a raised risk estimate with past atopic conditions. On the other hand, whether any of these hypotheses is relevant for children depends on grade 1 gliomas having similar immunosuppressive effects as grade 4 gliomas which seems unlikely but is largely unknown. Another low-grade tumor, meningioma, did not show an inverse relationship between atopic disease and tumor incidence in adults [7]. In addition, two recent studies of glioma in adults found an inverse association between prediagnostic IgE levels and glioma risk [19, 23], one of which [19] measured IgE levels as early as 20 years before diagnosis which speak against reverse causation. In the current study, however, we found an indication of reduced risk estimates associated with current atopic conditions, which was accompanied with raised risk estimates for past atopic conditions. These findings were, however, based on small numbers of subjects in the subgroups, and may also be explained by random variation. In addition, an ongoing chemo- and/or radiation therapy may affect the manifestation of atopic conditions [24], which could possibly affect recall when reporting about a history of atopic diseases.

To our knowledge, the association between allergic rhinitis, also known as hay fever, and brain tumor development has not previously been studied in children. We found a reduced risk primarily in the group 'other brain tumors', but not for glioma. Studies in adults have shown an inverse association between allergic rhinitis and glioma [6, 25], although not consistently [26].

The strengths of our study are the population-based control selection, identification of cases through high-quality population-based cancer registers and close collaboration with pediatric oncology and neurosurgery clinics, a detailed structured interviewer-administered questionnaire, and collection of extensive information on covariates. Recall bias caused by mental modifications could be reduced to a minimum because questions were answered by both the child and the parents together.

However, some limitations should be considered. The study had relatively high response rates, but we were nevertheless unable to recruit 29% of the selected controls and 17% of the eligible cases. Nonparticipation would not influence study results unless prevalence of atopic conditions are believed to differ between the included and non-included controls in a different manner than between included and nonincluded cases. Due to the roughly comparable participation rates, this seems very unlikely. Other limitations common to case–control studies is the risk of misclassification of exposure history. As in previous studies on children and adults, we measured atopic conditions through self-reports, which may be subject to misclassification errors and could lead to a dilution of risk estimates, if independent of case–control status. Obtaining a brain tumor diagnosis is a severe life-threatening event and may result in underreporting of atopic conditions in cases but not controls, which would explain decreased ORs for current atopic conditions but not increased odds ratios for past conditions. The reported prevalence of atopic conditions in our study is in accordance with other studies [10, 27]. In studies of self-reported atopic conditions in adults, the sensitivity for the question about self-reported asthma in relation to a clinical diagnosis of asthma was 68% in the reviewed studies (range 48–100%), and the specificity was 94% (range 78–100%) [28].

In conclusion, our results do not support an association between atopic conditions and risk of brain tumors overall in children and adolescents or of glioma in particular. Results stratified on current or past atopic conditions indicated a possibility of reverse causality, but these subgroup findings may also be explained by random variation. Only a few studies on atopic conditions and pediatric brain tumors are currently available, and the evidence is conflicting.

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disclosure

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